REMARKS

Initially, the Examiner is requested to note that there is a typographical error at page 13 of the Amendment filed November 6, 2003. That is, the last paragraph at page 13 should have read as follows:

> "The phosphorothioate derivatives of 8-halo-cAMP taught in Cho-Chung et al include all cAMPS compounds and an 8-substituted halogen, i.e., fluoride, chloride, bromium, iodine or astatin. Further, there is no teaching in Cho-Chung et al of the diastereomer (Rp or Sp), as claimed in the present application. The family members encompassed by the genus of Cho-Chung et al may thus, include Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS, Rp-8-I-cAMPS, Rp-8-F-cAMPS, Rp-8-At-cAMPS, Sp-8-Br-cAMPS, Sp-8-Cl-cAMPS, Sp-8-I-cAMPS, Sp-8-F-cAMPS, Sp-8-At-cAMPS. Furthermore, the term "phosphorothioates" also encompasses phosphorodithioates, i.e., Sp-8-Br-cAMPS2, Sp-8-Cl-cAMPS2, Sp-8-I-cAMPS2, Sp-8-F-cAMPS2, Sp-8-At-cAMPS2 would also be in the group. In total, this group has 15 members and the genus is not inherently limited to only a small number of compounds. As such, the specific compounds recited in Claims 40-44 are not disclosed in Cho-Chung et al.

On page 2 of the Office Action, the Examiner contends that the Oath or Declaration is defective because changes have been made to the date section for the signature of inventor Muller, but the changes have not been initialed.

Applicants respectfully submit that the Examiner's objection to the Declaration is in error since the change is clearly by Mr. Muller, i.e., he has crossed-out his signature and inserted the date therefore, as he initially placed his signature on the wrong line.

Nonetheless, this objection is believed to be obviated by the attached Substitute Declaration and Power of Attorney.

Claims 40, 43, 45 and 48-49 are now pending.

Claim 40 has been amended to delete the embodiment of Claim 41, thereby resulting in the cancellation of Claim 41. Further, Claim 40 has been amended to include the recitation of Claim 42 therein, thereby resulting in the cancellation of Claim 42.

Claim 43 has been amended to delete the embodiment of Claim 44, thereby resulting in the cancellation of Claim 44.

Claim 45 has been amended to include the recitation of Claims 47 and 51 therein, thereby resulting in the cancellation of Claims 47 and 51.

Claim 48 has been amended to correct the dependency in view of the amendments to Claim 45 and the cancellation of Claim 47.

Hence, the amendments to the claims do not constitute new matter, nor raise any new issues, and thus entry is requested.

On page 3 of the Office Action, the Examiner rejects Claims 40-42 under 35 U.S.C. § 102(b) as being anticipated by Gjertsen et al for the reason of record.

Specifically, the Examiner notes Applicants' arguments that the compositions disclosed by Gjertsen et al are not pharmaceutical compositions, because the compositions thereof were merely used *in vitro*. Further, the Examiner notes Applicants' arguments that the compounds used to make the compositions disclosed in Gjertsen et al were purchased from BIOLOG Life Sciences, and that Applicants have provided a Declaration indicating that these compounds may contain trace amounts of impurities and are not produced under GMP conditions, and therefore are not suitable for pharmaceutical use, and contain no filler or buffer. Finally, the Examiner notes Applicants' arguments that, in the instant application, the

compositions were treated to make them suitable for use as pharmaceuticals, whereas the compositions of Gjertsen et al were not so treated.

However, the Examiner contends that these arguments are not persuasive since the claims do not recite that the composition is endotoxin free and produced in a GMP setting.

Moreover, the Examiner contends that the compositions disclosed by Gjertsen et al can be used for pharmaceutical purposes as evidenced by Punch et al, which used the compounds disclosed by Gjertsen et al and purchased from BIOLOG Life Sciences with the only additional treatment being the addition of phosphate buffered saline. The Examiner contends that the additional steps set forth in Applicants' arguments, i.e., removal of endotoxin and preparation in a GMP setting, were not required, as the clinical experiments in Punch et al were performed on rats.

The Examiner notes that Punch et al did not use the same analogues as claimed. However, the Examiner contends that the other analogues used in Gjertsen et al and supplied by BIOLOG Life Sciences were in the same form as the claimed analogues that were supplied to Gjertsen et al. The Examiner contends that Punch et al illustrates that cAMPS compounds in the form supplied by BIOLOG Life Sciences as disclosed by Gjertsen et al are actually for use *in vivo*.

The Examiner further notes that while the cAMPS compounds supplied by BIOLOG Life Sciences may not be appropriate for use in a clinical setting in a human, they are useful for *in vivo* in animal studies, which is encompassed by the claimed expression "pharmaceutical".

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

In view of the amendment to Claim 40, to recite that the composition is useful for treating "AIDS, HIV or CVI in humans", Applicants respectfully submit that the Examiner's rejection has been rendered moot. Note, support for this amendment can be found, *inter alia*, at pages 1-3 of the present application. In particular, page 3 refers to the treatment of HIV and CVI patients, and page 2 refers to "young adults". By this amendment, it is clear that the composition is endotoxin free and produced in a GMP setting, otherwise it could not be used in humans.

The Examiner is requested to note that, in the present invention, Applicants have identified a new mechanism for the treatment of immunosuppressive diseases. Prior to the present invention, the role of cAMP levels in T cell proliferation and immune responses in physiological conditions was not known and the role of specific PKA isozymes in T cell functioning had not been elucidated. The present invention deals with the identification and utilization of PKA isozyme specific cAMP antagonists and the contribution to the art is the identification of a specific isozyme target.

Moreover, the Declaration from Dr. Hans-Gotfried Genieser should be given significant weight. Dr. Genieser is the owner, president and chief executive of BIOLOG Life Science Institute, and is therefore extremely familiar with the products and the particular uses for which they are suitable and for which they are sold. Dr. Genieser's statements that the compounds are not for *in vivo* use and are not pharmaceutical compositions should be more persuasive than an indication in an article

(Punch et al) that a laboratory animal was administered the compounds, tested and then sacrificed. A compound suitable for pharmaceutical use in humans must carry with it more than just that the compound can be solubilized and injected in a living animal. For use in humans, where viability is to be maintained (unlike in the animals of Punch et al which were sacrificed) it is imperative that contaminants are removed and that the compositions are compatible with long term use. Dr. Genieser has confirmed that the BIOLOG compounds do not satisfy this requirement, and thus can not be considered pharmaceutical compositions, i.e., compositions for use in humans. Moreover, Gjertsen et al provides no teaching or suggestion that the compounds thereof could be used medically, and thus provides no motivation to generate pharmaceutical compositions.

In any event, the Examiner is requested to note that Claim 40 has also been amended to delete reference to Rp-8-Br-cAMPS taught in Gjersten et al, thereby further obviating the Examiner's rejection.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Gjersten et al, and thus request withdrawal of the Examiner's rejection.

On page 6 of the Office Action, the Examiner rejects Claims 40-44 under 35 U.S.C. § 102(e) as being anticipated by Cho-Chung et al for the reasons of record.

Specifically, the Examiner states that Applicants argue that Cho-Chung et al discloses generally phosphorothioate derivatives of 8-halo-cAMP, including all cAMPS compounds, that this general disclosure constitutes a large genus of 15 compounds, and the genus is not inherently limited to a small

number of compounds. Hence, Applicants argue that the specific compounds as claimed are not disclosed in Cho-Chung et al.

However, the Examiner contends that this argument is not found persuasive because Cho-Chung et al specifically discloses preferable phosphorothioate derivatives of 8-halo-cAMPS, which constitutes a genus of only two compounds, i.e., Sp-8-Br-cAMPS and Rp-8-Br-cAMPS, which is inherently a very small number of compounds. Further, the Examiner states that even if the genus was extended to include phosphorodithioates as suggested by Applicants, that genus is also very small and only adds two more compounds.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Cho-Chung et al does not provide any teaching that would lead the skilled person to the compositions of Claims 40 and 43. These compositions contain cAMP antagonists which may be used to inhibit PKAIα and which may therefore, as a result of Applicants' investigations, be used to treat HIV, CVI and AIDS. This is not apparent from the teaching of Cho-Chung et al, which deals with inhibition of cell proliferation, in order to regulate abnormal cell growth. As mentioned above, the identification of PKAIα as a pivotal target molecule for HIV and AIDS has allowed Applicants to identify and develop a treatment for these diseases by identifying suitable compounds for treatment.

Cho-Chung et al is concerned with a different type of treatment and there is no reason to expect that the specific molecules claimed in Claims 40 and 43 would prove useful compounds for a purpose in which Cho-Chung et al is not interested in. Also, there is no teaching in Cho-Chung et al

of the selection of cAMP antagonists, such as those recited in Claim 40. Further, with regard to Claim 43, this concerns a method of inhibiting PKA type Iα. Cho-Chung et al does not teach anything about this isozyme or method, and thus this claim is clearly not anticipated by Cho-Chung et al.

In any event, in view of the amendments to Claims 40 and 43 to delete reference to Rp-8-Br-cAMPS, Applicants respectfully submit that the Examiner's rejection has been rendered moot.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Chuo-Chung et al, and thus request withdrawal of the Examiner's rejection.

Finally, on page 7 of the Office Action, the Examiner rejects Claims 40-45 and 47-49 and new Claims 51 under 35 U.S.C. § 112, first paragraph for the reasons of record.

Specifically, the Examiner notes Applicants' arguments that Gjertsen et al does not support the assertion that the activity of the antagonists of the claims is unpredictable. Further, the Examiner notes Applicants' argument that the compounds do not need to be tested to meet the standard for enablement, i.e., Applicants have demonstrated efficacy for a significant number of claimed compounds and each of the claimed compounds has been shown to have some efficacy *in vitro*.

However, the Examiner contends that this argument is not found persuasive since Gjertsen et al demonstrates that the various compounds and the claimed methods have different abilities to inhibit the target enzyme, and given this difference in efficacy, it would be unpredictable that each of the compounds, as claimed, would be as efficacious *in vivo* as required by the claimed methods, and it would be unpredictable

that they would achieve the degree of inhibition required to provide the treatment effects required by the claimed methods. The Examiner notes that Applicants have demonstrated inhibition *in vitro*. However, the Examiner contends that it is unclear that such would correlate with efficacy *in vivo* and result in a treatment effect for the broad range of diseases encompassed by the claims.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

In the First Declaration filed in June 19, 2002, data was provided which shows that the claimed compositions work as anticipated, and that MAIDS mice (which have an immunosuppressive disorder), exhibit enhanced T cell function on treatment with a cAMP antagonist (Rp-8-Br-cAMPS). These results are indicative of the *in vivo* effects of cAMP antagonists, and this animal model supports the utility of such compounds in human and other animals.

Figure 1 of this Declaration shows the effect of Rp-8-Br-cAMPS on tritiated thymidine incorporation in T cells activated by cross-litigation of anti-CD3. MAIDS mice who received this compound for 14 days had a T cell immune response to anti-CD3 that was increased more than 3-fold compared to untreated mice. This brought the level of immune response to levels comparable to those of cells from healthy mice.

Results are also shown in this First Declaration *in vitro* for other cAMPS antagonists. Table 2 of this Declaration shows that *in vitro*, Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS and Rp-8-Br-monobutyryl-cAMPS are all effective at reversing the inhibitory effect of a fixed dose of cAMP agonist, which mimics

the situation in HIV T cells, on T cell function. Similar effects would be expected *in vivo*.

It is to be noted that following the submission of this Declaration, the Examiner acknowledged that the specification is enabling for use of Rp-8-Cl-cAMPS, Rp-8-Br-cAMPS and Rp-8-Br-monobutyryl-cAMPS in pharmaceutical compositions and in methods of treatment of CVI, AIDS or HIV infection for the inhibition of PKAIα (see page 2 of the Official Action of May 6, 2003).

The Second Declaration filed on November 6, 2003, showed the efficacy of Rp-8-piperidino-cAMPS, Rp-8-CPT-cAMPS, Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS *in vitro* as antagonists of PKAIα. The specification in Examples 1 and 2 also show work conducted *in vitro*, on T cells from HIV and CVI patients. Administration of Rp-8-Br-cAMPS in both cases resulted in enhanced T cell proliferation. The results in the specification and Declaration are summarized in the table below:

Experiment	Compound tested	Result	Results Presented
In vivo on MAIDS mice	Rp-8-Br-cAMPS	Enhanced T cell function	Declaration filed June 19, 2002
In vitro on human T cells	Rp-8-Br-cAMPS	Enhanced T cell function	Declaration filed June 19, 2002
	Rp-8-Cl-cAMPS	Enhanced T cell function	Declaration filed June 19, 2002
	Rp-8-Br-monobutyryl-cAMPS	Enhanced T cell function	Declaration filed June 19, 2002
In vitro on PKA RIα holoenzyme	Rp-8-CPT-cAMPS Rp-8-Br-cAMPS Rp-8-Cl-cAMPS Rp-8-piperidino-cAMPS	Exhibit antagonist action on enzyme	Declaration filed November 6, 2003
In vitro on T cells from HIV patients	Rp-8-Br-cAMPS	Enhanced T cell proliferation	Specification, Example 1, pages 20-22
In vitro on T cells from CVI patients	Rp-8-Br-cAMPS	Enhanced T cell proliferation	Specification, Example 2, page 27

It is therefore clear that a significant amount of supporting evidence has been provided. Both *in vivo* and *in vitro* evidence has been provided and, in particular, actual evidence of efficacy or likely efficacy has been shown for each antagonist specifically claimed.

While it is apparent from Gjertsen et al that not all compounds work equally well to inhibit PKA I and II, only Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS and Rp-N^6-phenyl-cAMPS were tested therein to any rigorous degree. The initial experiment that was performed was a screen for identifying potentially useful agents; the ability of the compounds to antagonize glucagon induced lowering of DNA replication in hepatocytes was assayed (glucagon is a cAMP elevating agent). This assay is useful to identify potent and cell permeable antagonists, but is not suitable to identify weak antagonists, nor does it distinguish between antagonists of PKA types I and II.

In Figure 3 of Gjertsen et al, all of the compounds tested are said to be antagonists of PKA I. Figure 3A shows Rp-cAMPS, Rp-8-Cl-cAMPS, Rp-8-Br-cAMPS and Rp-N^6-phenyl-cAMPS all antagonize PKA type I. In Figure 1, however, Rp-N^6-phenyl-cAMPS is shown not to function as an antagonist of forskolin-induced cAMP actions in fibroblasts. There is thus, contradiction within Gjertsen et al as different results appear to be achieved by different methods. Hence, there is no clear data in Gjertsen et al that would support the Examiner's assertion of the unpredictability of the antagonist properties of these compounds.

Gjertsen et al is concerned with finding the most potent antagonist, and refers in this regard to the "first line" cAMP antagonist. This is not to say, much less demonstrate, that

other compounds which are less potent, are not antagonists. Indeed, Gjertsen et al shows that not only it is easy to identify antagonists, but that a high proportion of cAMP analogues are antagonists. It should be noted that in no claim of the present application is reference made to a cAMP analogue *per se*. The claims of the present application refer to specific compounds or refer generically to a specific class of cAMP antagonists, i.e., Rp-8-substituted-cAMPS (see Claim 45). Thus, those compounds in Gjertsen et al which are cAMP analogues, but are not cAMP antagonists, are clearly outside of the scope of the present claims. Hence, the relevant teaching of Gjertsen et al may be distilled to the fact that antagonists of cAMP have variable potency. This is not contested. The fact that antagonistic activity is present inherently confers the ability to antagonize, and thus reduce PKA Type Iα signaling. In view of Applicants' discovery of the pivotal role of PKA Type Iα signaling in immunosuppressive diseases, the use of such antagonists to affect that signaling *in vitro* or *in vivo* is thus fully expected to elicit the desired increase in T cell function. This is readily testable for individual antagonists, and has been borne out by a representative number of antagonists in the Declaration evidence filed June 19, 2002.

As noted above, Applicants have already shown the efficacy of Rp-8-Br-, Rp-8-Cl-, and Rp-8-Br-monobutyryl-cAMP analogues (see the Declaration evidence of record). Other compounds specifically mentioned in the claims are Rp-8-(4-chlorophenylthio)- and Rp-piperidino- cAMP analogues. The antagonistic capabilities of these compounds has now also been tested (as well as the Rp-8-Br- and Rp-8-Cl- cAMP analogues for comparative purposes). The Second Declaration provides

data, which shows that Rp-8-Cl-cAMPS, Rp-8-Br-cAMPS, Rp-8-PIP-cAMPS, Rp-8-CPT-cAMPS and Rp-cAMPS all act as antagonists of PKAIα. Rp-cAMPS has been tested instead of Rp-monobutyryl-cAMPS, as the former is the physiologically relevant form, in view of the cleavage to remove the monobutyryl moiety within the cell. Further information is also included in the Second Declaration showing the specificity of these compounds (EC_{50} values, see the figures of the Second Declaration). Comparable *in vivo* results to those already shown, e.g., for the Rp-8-Br-cAMPS may also be expected for these antagonists.

While the Examiner has contended that one necessarily would practice *de novo* "trial and error" experimentation to make and use cAMPS analogs other than Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS and Rp-8-Br-monobutyryl-cAMPS, this is not the standard for lack of enablment. The standard is whether or not it would require "undue" experimentation. Trial and error experimentation may be routine, and therefore not undue. In the context of the present invention, such would be simply routine experimentation.

Indeed this type of assay is set out in Gjertsen et al, see Figure 3 and the associated text. It is a relatively straightforward assay to perform and certainly could not be seen as undue experimentation. The Examples in the present application provide further types of assay that could be performed (e.g., testing T cell proliferation).

Hence, Applicants respectfully submit that the Examiner's rejection is improper.

In summary, as to claims directed to specific compounds, direct evidence of the antagonistic effect of each claimed compound has been provided. Direct evidence of *in vitro* efficacy of 3 of the 6 named compounds has been shown and

directly supports the fact that the PKA Type Iα signaling is affected by these compounds. Further, it has been shown that the desired effects are achieved *in vivo* with a representative compound. There is absolutely no evidence to suggest that any of the other specifically recited compounds will not achieve the expected effects *in vivo*. The compounds belong to a small closely related family, all of which are Rp-cAMPS compounds. In view of their strong structural similarity, and extensive supporting data for all, or at least a representative set of the claimed compounds, which could be further examined by well described methods without undue experimentation, Applicants respectfully submit the requirements for enablement have been fully and comprehensively met.

It should be noted with regard to Claim 43, all that is required is that the effects of PKA Type Iα signaling are mediated. Since all of the compounds claimed in Claim 43 have specifically been tested and found to have antagonistic activity for that enzyme, full enablement for this particular use has been shown.

With regard to somewhat more general Claim 45, as mentioned above, only a specific class of cAMP antagonists is claimed, and Applicants have shown as noted above, that these antagonists fulfill their promise both *in vitro* and *in vivo*. The identification and testing of compounds within that family is readily achievable. Applicants have identified the crucial role of PKA Type Iα in the pathology of immunosuppressive disorders. They thus, offer for the first time, a means of treating such disorders which requires antagonism of the identified signaling pathway. As such, the claim scope is entirely commensurate with the invention which has been made. Several examples of suitable

compounds for this purpose have been shown to be effective. Further, related compounds can be readily and routinely identified by the skilled person. The present application thus, provides the information and methods necessary to identify and test for suitable compounds without undue experimentation.

Note, Claim 45 has been amended to recite cAMP antagonists that are Rp-8-substituted-cAMPS. This is a relatively small class of compounds and efficacy has been shown for what should be considered a representative number of compounds from this class. It is well-settled law that providing a representative number of examples are shown to be of use according to the invention, is sufficient to show enablement. To require evidence of each and every member of a defined family in an enormous and onerous burden on Applicants and not one that is legally required.

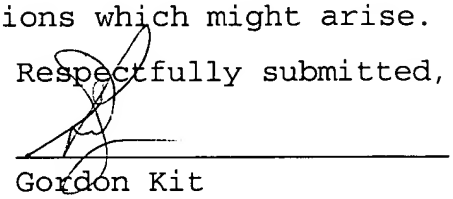
Accordingly, Applicants respectfully submit that claims are enabled by the present specification, and thus request withdrawal of the Examiner's rejection.

The Examiner is requested to note that it appears that the copy of Hofmann et al submitted with Form PTO-1449 on March 3, 2004, may have been incomplete. Therefore, Applicants resubmit herewith a complete copy of Hofmann et al (along with a copy of Form PTO-1449 and the date-stamped mailroom receipt hereto). The Examiner is respectfully request to acknowledge receipt of said reference in the next official action

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,



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